News

New antibiotics effective against resistant bacteria

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Abstract

New antibiotics that use a two-pronged approach to kill bacteria have been discovered. These dual-acting antibiotics attack a key pathway, the methyl-D-erythritol phosphate pathway, within the bacteria via enzyme inhibition. This leads not only to essential disruption of processes within the bacterium (e.g., respiration), but also causes a build-up of pathogen-associated molecular patterns. The increased presence of these molecular pathogens leads to a more pronounced immune response to the pathogen. By utilising two methods of attack, this type of antibiotic is more than twice as effective at killing some resistant strains of bacteria compared to regular, world-class antibiotics.

Abbreviations

DAIA - Dual-acting immune-antibiotics
IspH - 4-Hydroxy-3-methylbut-2-enly diphosphate reductase
S - Svedberg units

Introduction

Antibiotics kill bacteria by acting on processes such as cell wall synthesis or DNA replication. Disrupting these processes leads to cell death by causing structural damage or preventing RNA synthesis.[1] Their discovery revolutionised healthcare, improving the survivability of infections like bronchitis,[2] increasing life expectancy substantially.[3] Bacteria can become resistant by preventing an antibiotic acting on it via a genetic mutation or gaining new DNA. An example is tetracycline, which stops protein synthesis in target bacteria by binding to the 30s subunit of the ribosome, preventing RNA interacting with it, therefore, preventing new amino acids being added to the protein chain.[4] Strains resistant to tetracycline arise due to genes like tetM. This gene creates a protein which allows the ribosome to interact with transfer RNA in a stable manner despite the presence of tetracycline.[5] **Figure 1** shows how a bacteria cell could become resistant to tetracycline. Significant resistant strains include penicillin-resistant Staphylococcus which causes pneumonia and vancomycin-resistant Enterococci. More dangerously, superbugs (bacteria which have developed resistance to nearly all antibiotics in use) can emerge. Infections from resistant bacteria cause at least 35,000 deaths a year in the US.[6] By 2050, early deaths due to antibiotic resistance are set to swell to 10 million each year;[7] clearly this crisis could have devastating impacts.

The new class of antibiotic

The Witstar Institute has made a new discovery to help target resistant bacteria, which harnesses a two-front approach and works in conjunction with the host's immune system. The presence of pathogens leads to antigen presenting via antigen presenting cells, causing T cell responses which help kill bacteria. The T-cells instigate microptosis (programmed bacteria death) within the cell by conveying granzymes within the bacterium which disrupt essential processes.[8] The Wistar Institute has harnessed this process as well as antibiotic action via dual-acting immune-antibiotics (DAIAs) to kill bacteria. Firstly, the DAIA attacks the bacteria on an essential bacterial pathway absent in humans: the methyl-D-erythritol phosphate pathway. Within this pathway it inhibits key enzymes: IspH producing terpenoids. These chemicals have essential involvement in processes like respiration and cell wall synthesis. The second prong of attack acts via the immune system. Enzyme inhibition by the DAIAs has a secondary impact: it causes a build-up of pathogen-associated molecular patterns, making the bacteria more visible to the immune system. This causes T cells to multiply and create proteins like granzymes which kill the bacterium. The action of DAIAs is shown in **Figure 2**. After testing this approach on drug resistant bacteria derivatives of cholera and pneumonia a lower dose of this drug is needed to prevent the growth of 90% of the bacteria in a colony compared to world class antibiotics. In vitro, the DAIA can leave less than half the number of cholera bacteria than current antibiotics, such as cefepime. Clearly, this antibiotic could be very effective.

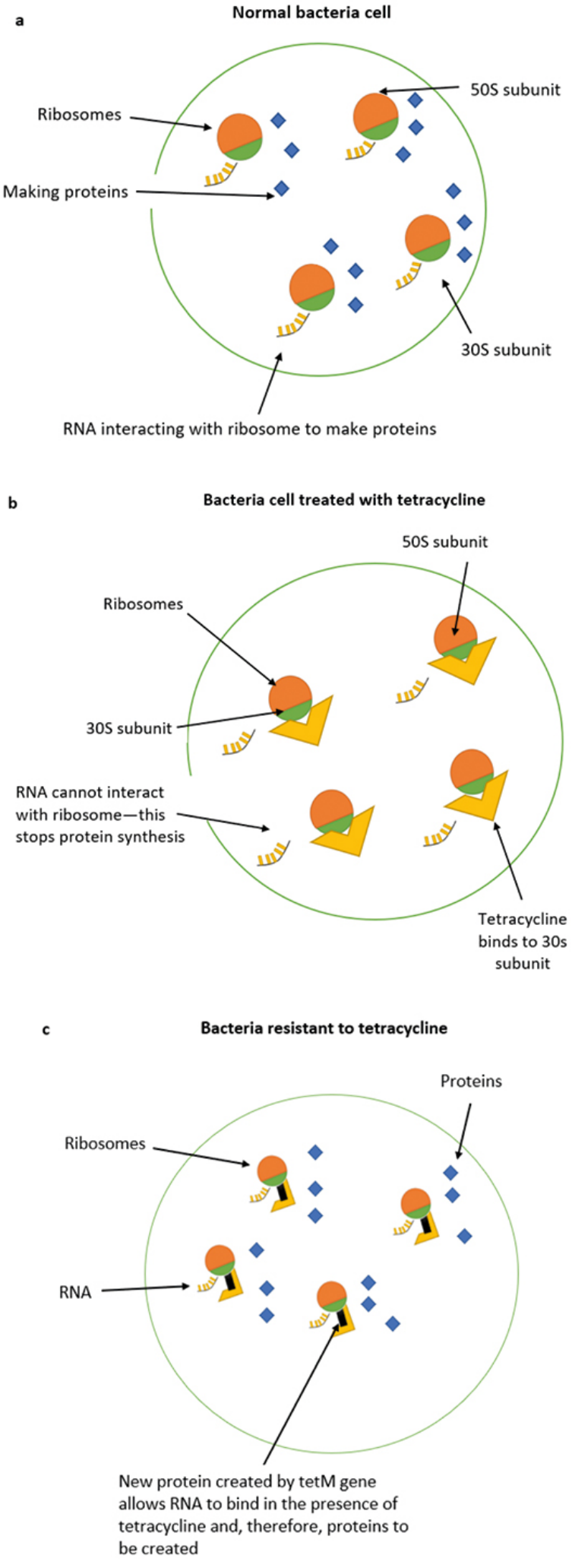

Figure 1. Illustration of (a) how a normal bacteria cell functions and produces proteins, (b) how this is stopped in the presence of the antibiotic tetracycline and (c) how bacteria cells could become resistant to the antibiotic.

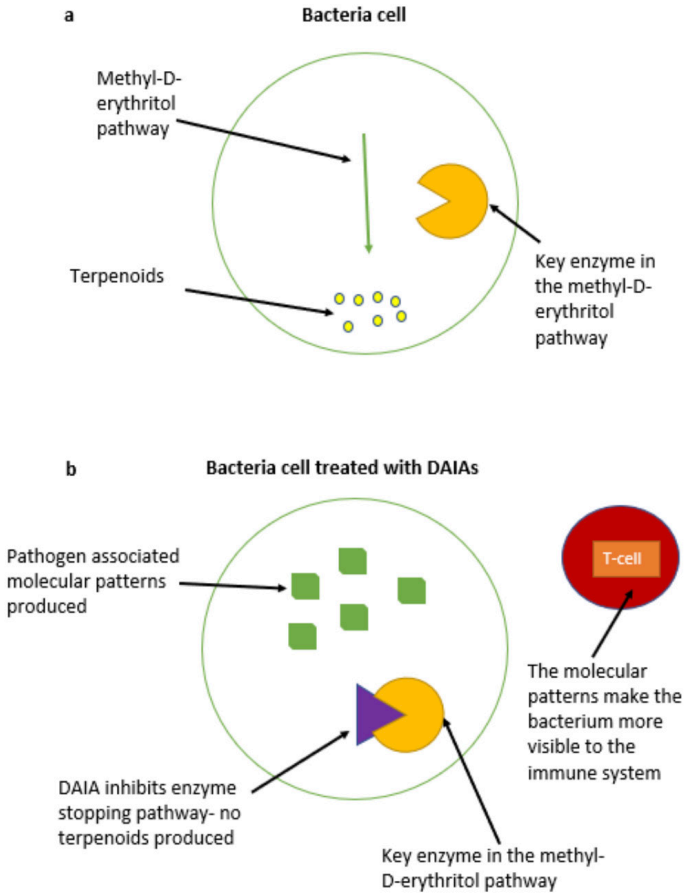

Figure 2. (a) The normal functioning of the methyl-D-ethythritol pathway in bacteria cells and (b) how this changes when cells are treated with DAIAs.

For 9 out of the 11 new antibiotics approved between 2017 and 2020 it is very likely that bacteria will quickly become resistant to them. This is because they are derived from existing classes of antibiotic where resistance mechanisms are established.[9] Cefiderocol was one of the new antibiotics approved. It is effective against strains of multi drug resistant bacteria, acting by inhibiting penicillin-binding proteins and preventing cell wall synthesis thus causing the death of the bacteria. However, scientists have discovered resistance to cefiderocol.[10] DAIAs attack bacteria on two fronts, via the immune system and the methyl-D-erythritol pathway which should make it more difficult for bacteria to develop resistance. Furthermore, there is a reduced chance bacteria have evolved to become resistant to this antibiotic due to the fact IspH inhibitors haven't yet been discovered in microorganisms, meaning bacteria haven't evolved to live without this pathway.[8] However, in my opinion, if T-cell action is an integral part of this antibiotic, individuals who have immunodeficiencies and consequently a depleted number of T-cells may struggle to produce a pronounced immune response to attack the bacteria.

There are some other dual acting antibiotics in development, however they consist of two antibiotics joined into one compound. An example is the rifamycin-quinolone hybrid. It attacks the bacteria using combined effects of both antibiotics, inhibiting RNA polymerase and activity against DNA gyrase and DNA topoisomerase, respectively. In studies it has demonstrated activity against pathogens like staphylococcus, including resistant populations. The antibiotic kills via quinolone effects against pathogens that are resistant to rifamycin, but with decreased efficacy at higher concentrations.[11] This is different to the DAIAs as, if bacteria become resistant and prevent enzyme inhibition neither the direct killing nor the immune response would occur because they both occur due to enzyme inhibition. However, when using two antibiotics there is the risk pathogens will become resistant to both.

Conclusion

The discovery of these new antibiotics is very promising, in that they could treat infections of resistant strains of bacteria. However, to keep these new antibiotics as viable weapons in the arsenal against antimicrobial resistance, their use will have to be controlled to reduce risk of bacteria acquiring mutations and becoming resistant to them.

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